THESIS

FOR THE AWARD OF DEGREE OF

DOCTOR OF MEDICINE

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"TO STUDY IRON PROFILE IN DIABETES MELLITUS AND ITS RELATION WITH HbA1c"

DR. PRABHJOT SINGH

SANTOSH DEEMED TO BE UNIVERSITY
NO. 1, SANTOSH NAGAR,
GHAZIABAD-201009, NCR DELHI, INDIA

DEPARTMENT OF GENERAL MEDICINE
SANTOSH MEDICAL COLLEGE & HOSPITAL
GHAZIABAD, NCR DELHI

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Guide

Dr**. Shivani Bansal**
Professor
Department of General Medicine
Santosh Medical College & Hospital
Ghaziabad (U.P.), India

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Co-Guide

Dr. Abhishek Pathre
Assistant professor
Department of pathology
Santosh Medical College & Hospital
Ghaziabad (UP), India

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PROF. (Dr.) Ashok kumar

M.B.B.S., M.D.
Professor & Head
Department of General Medicine
Santosh Medical College & Hospital
Ghaziabad – 201001 (U.P.)

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Dr Alka Agrawal

Dean
Faculty of Medical Sciences
Santosh Medical College & Hospital
Santosh Deemed to be University
Ghaziabad – 201001 (U.P.)

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Dr. Jyoti Batra

Dean Research

Santosh Medical College & Hospital

Santosh Deemed to be University

Ghaziabad – 201001(U.P.)

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1. Project is considered to be absolutely essential for the advancement of knowledge and for the benefit of all.
2. Only subjects who volunteer for the project will be included. Their informed consent shall be obtained prior to commencement of the research project and subjects will be kept fully appraised of all consequences.
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7. Research reports, materials and data will be preserved (as per institutional guidelines).
8. Result of research will be made known through scientific publications and scientific presentations.
9. Professional and moral responsibilities will be of the researchers, directly or indirectly connected with the research.
10. Standard of care will be provided to the subjects at all times during their involvement with the research and no extra investigations will be conducted on the patients as part of this research

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INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. DM has several categories, including type 1, type 2, maturity-onset diabetes of the young (MODY), gestational diabetes, neonatal diabetes, and secondary causes due to endocrinopathies, steroid use etc. Hemoglobin A1C (HbA1c) is glycated haemoglobin that is used as an indicator of a patient's glycemic status over the previous three months. [1]

Glycated hemoglobin (HbA1c) is a type of hemoglobin that has a stable adduct of glucose linked covalently to the N-terminal valine of the -chain. Normal adult hemoglobin is composed of HbA (22), HbA2 (22), and HbF (22) in proportions of 97%, 2.5%, and 0.5%, respectively. Roughly six per cent of the total HbA is designated as HbA1, also known as HbA1. HbA1 is made up of subunits designated as HbA1a1, HbA1a2, HbA1b, and HbA1c. These fractions are distinguished from one another by the distinct electrophoretic and chromatographic properties that they each possess.

These fractions differ slightly in their electrophoretic and chromatographic properties from those of the major component, HbA1c, despite the fact that HbA1 and HbA0 have identical sequences of amino acids. The majority of people have a level of HbA1c in their blood. [2] It makes up about five per cent of the total HbA fraction in individuals who are healthy. There is currently no evidence that HbA1c serves any physiologic purpose. Chronic hyperglycemia, which leads to complications that are unique to diabetes, is the defining characteristic of diabetes. The HbA1c, which represents long-term glucose exposure, therefore predicts diabetes-specific complications more accurately than a single glucose measurement. Studies demonstrated a consistent and significant correlation between retinopathy and HbA1c levels, rather than the correlation between retinopathy and fasting glucose levels. [3] Multiple controlled clinical trials and a large volume of data from various populations have provided strong evidence for assigning an HbA1c cut-off point of more than 6.5% for diabetes diagnosis, as this HbA1c level is associated with an increased prevalence of diabetes-specific complications, particularly retinopathy. [4]This cut-off point is not a definitive boundary between diabetes and normal glycemic status; instead, it serves as a guideline. However, this level is accurate and focused on identifying patients who are at risk for retinopathy. Diabetes is diagnosed when the HbA1c level is greater than 6.5%, according to the International Expert Committee. The same was confirmed by the American Diabetes Association. [5].However, this diagnostic HbA1c test should be performed using a method certified by the NGSP- National Glycohemoglobin Standardization Program and traceable to the Diabetes

Control and Complications Trial (DCCT)V reference assay.

[6]This may be because glycosylated Hb is attached to the Red blood cell (RBC) surface and s tays there for 3to4 months. Therefore, the values of HbA1c indicate the previously averaged glucose levels for three to four months. However, any nutritional deficiency or haemoglobin variant can change the number, surface area, and size of the RBC, affecting the attachment of glycosylated Hb and its values. [7-10]Determining whether or not this association exists may be very helpful in concurrently mon itoring the diabetic status and the anaemic status of patients.Iron deficiency is a condition in which the iron content of the body falls below normal levels. The first stage of iron deficiency is iron store depletion, in which serum iron, transferrin saturation, and haemoglobin levels are normal, but iron storage is reduced or absent. The subsequent stage is iron deficiency without anemia, which is marked by depleted iron stores, low serum iron, and transferrin saturation, but not anemia. [11] Anemia due to iron deficiency is the farthest progressed stage of iron deficiency. It is distinguished by the lack of iron stores, low serum iron levels, and low transferrin saturation, in addition to low hemoglobin levels. In regions where meat consumption is low, food is not fortified with iron, malaria, intestinal infections, and parasitic worms are prevalent, and women and children are disproportionately affected by iron deficiency anemia. Serum ferritin concentration represents total body iron stores. It is possible for the serum ferritin level to drop as low as 10 mcg/L when a person has iron deficiency. In inflammatory disorders such as rheumatoid arthritis, chronic kidney disease, and malignancies, the ferritin concentration is significantly increased. The normal range for serum ferritin varies depending on the individual's age as well as their gender. [12]

Aim and Objectives

Aims

1. To study effect of iron deficiency anemia in patients suffering from diabetes mellitus

Objectives

1. To observe and analyze the effect of RBC indices on HbA1c in diabetics

2. To study how HbA1c is a crucial marker for diagnosing diabetes and in deciding treatment plan

Review of Literature

Diabetes mellitus is a serious condition that can last for a long time (also known as "chronic") and is characterized by abnormally high blood levels of glucose in the blood. This condition occurs when the body is unable to produce any or enough of the hormone insulin, or when it is unable to use the insulin have it does produce in an efficient manner. The pancreas is responsible for the production of the vital hormone known as insulin. It enables glucose to enter the cells of the body from the bloodstream, where it can either be converted into energy or stored. The breakdown of protein and fat both require insulin for proper functioning. A deficiency in insulin or an inability of cells to respond to insulin can cause elevated levels of glucose in the blood. Diabetes, particularly when it is poorly controlled, can lead to complications such as nephropathy, retinopathy, and neuropathy. It can also lead to several disordered metabolic processes, including oxidative stress, which causes oxidative damage to tissues and cells. Patients with diabetes are at an increased risk for various developing a variety of blood disorders, including anemia [14]. Anemia is most commonly seen in diabetic patients who also suffer from renal insufficiency, according to the findings of a large number of research studies [15]. A number of additional studies have also reported an incidence of anemia in diabetic patients prior to the manifestation of renal Impairment. Patients suffering from diabetic nephropathy experience anemia at an earlier stage and to a greater degree than patients suffering from other causes of renal failure [16].

It is estimated that 74,194.7% of people have diabetes, with a comparative diabetes prevalence that is 9.6 when adjusted for age. The number of people who have diabetes that has not been diagnosed is estimated to be 39,397.4%, making the proportion of people who have diabetes that has not been diagnosed 53.1.

According to the National Family Health Survey-5 for 2021, 6% of women aged 15 and older have a high blood glucose level (141-160 mg/Dl). This information comes from the study that was conducted in 2021. Another 6% of women have a blood glucose level that is extremely high (more than 160 mg/dl), which leaves 12% of women with a blood glucose level that is higher than 140 mg/dl. The prevalence of high blood glucose is slightly higher among men than it is among women. Seven percent of men aged 15 and older have high blood glucose, and another seven percent have very high blood glucose, for a total prevalence of fourteen percent among men. One percent of adults aged 15women and men, have normal blood sugar levels and take medication to reduce those levels and older, including both women and men, have normal blood sugar levels and take medication to bring those levels down.

Glycated hemoglobin [HbA1c]

Glycated hemoglobin, which is also referred to as glucohemoglobin, is the most accurate indicator of how well blood glucose levels have been controlled over the long term. Glycation is a process that occurs when a sugar residue is added to an amino group of a protein in a way that is not catalyzed by enzyme. Hemoglobin, plasma proteins, membrane proteins, lens proteins, etc., may undergo glycosylation. The significant fraction (80%) is composed of HbA1c. Glycation occurs at the N-terminal valine residue of each beta chain in the HbA1C molecule. The HbA1c test provides a retrospective index that is integrated plasma glucose values over a period of 6–8 weeks. This index is not susceptible to large fluctuations in plasma glucose levels. A reliable indicator of diabetes control over the past 90 days, the efficacy of treatment, and the risk of developing acute or long-term complications is the HbA1c level. [16] Once glucose has attached to hemoglobin, it cannot be detached again. As a consequence, it stays contained within the erythrocyte throughout the entirety of the RBC. [18]. Therefore, the HbA1c test ought to be carried out routinely in all patients who have diabetes in order to evaluate the level of glycemic control during the first visit, and then as a component of continuing visits once every three months in order to ascertain metabolic control. [17]

Diagnostic Criteria For Diabetes And Impaired Glucose Tolerance

The International Expert Committee with members appointed by the ADA, the European Association for the Study of Diabetes and the International Diabetes Federation has issued diagnostic criteria for DM based on the following premises:

Condition	2 hour glucose	Fasting glucose	HbA1C
	mg/dl	mg/dl	%
Normal	<140	<100	<5.6
Impaired glucose tolerance	140–199	100–125	5.7–6.4
Diabetes mellitus	≥200	≥126	≥6.5

Anemia

Anemia, which derives its name from the Greek words for "without blood" and "emia," refers to a condition in which the red blood cell count, hemoglobin levels, and/or hematocrit values are lower than normal. As a consequence, the blood is less able to deliver oxygen to the tissues of the body, which is known as anemia. Anemias that have normocytic and normochromic red cells as well as an abnormally low reticulocyte response (reticulocyte index of 2.5%) are considered to be hypoproliferative anemias. In this category are the conditions of early iron deficiency (before hypochromic microcytic red cells develop), acute and chronic inflammation (including many forms of cancer), and renal disease, hypo metabolic states such as protein malnutrition and endocrine deficiencies, and anemia caused by damage to the bone marrow. Iron deficiency is one of the most common forms of malnutrition. [19]

Iron deficiency anemia

Iron deficiency is the cause of approximately one million deaths a year across the world and is responsible for approximately half of all cases of anemia. North America only accounts for 1.4% of the total morbidity and mortality that is associated with iron deficiency. The majority of the global mortality burden is carried by Africa and parts of Asia. [20]

Hemoglobin Levels Below Which Women And Men Are Considered Anemic	
Respondents	Hemoglobin Level In Grams/Deciliter
Non-Pregnant Women Age 15-49	<11.0
Pregnant Women Age 15-49	<12.0
Men Age 15-49	<13.0
*Hemoglobin Levels Are Adjusted For Smoking, And For Altitude In Enumeration Areas That Are Above 1,000 Meters	

Causes of Anemia in Diabetes

- Restricting one's diet to foods with a high glycemic index and eating less as a result of having less of an appetite ,
- Lack of absorption as a result of diabetic Gastropathy and H. Pylori infections, which are common in diabetics,
- As a result of the release of inflammatory cytokines and oxidative free radicals.
- Increased Blood Loss caused by the Diabetic Foot's Failure to Heal.
- Anemia caused by a chronic disease
- Nephropathy caused by diabetes and a reduced production of erythropoietin

Stages of Iron Deficiency

There are three distinct stages that can be identified throughout the course of iron deficiency.

The ***initial stage*** is characterized by an inadequate supply of iron. The amount of iron that the body needs is greater than what it is able to absorb from the food that it eats. This is most likely the case because of increased iron losses that occur as a result of blood loss, pregnancy (during which the mother is unable to meet the iron demands of the growing fetus erythropoiesis), and adolescents who do not consume enough iron through their diet. In contrast to what the gut can absorb from a normal diet, the iron is mobilized from reticuloendothelial stores whenever there is blood loss of more than 10–20 ml of red cells per day. The levels of serum iron, total iron-binding capacity (TIBC), and red cell protoporphyrin all stay within normal ranges as long as there are iron stores present. Blood films taken from the periphery reveal normal red cell morphology and indices.

In the ***second stage,*** the erythropoiesis is iron-deficient, and moderate anemia is present (hemoglobin between 10 and 13 g/dL). When iron stores are depleted, the serum iron level will start to drop. The levels of TIBC as well as red cell protoporphyrin rise. The ferritin level in the serum is 15 mcg/L, which indicates that there is no iron stored in the marrow. Once the saturation of the transferrin reaches 15-20%,

The ***third stage*** is characterized by severe anemia (a hemoglobin level between 7 and 8 g/dL). Target cells and misshapen red cells (poikilocytes) appear in cigar- or pencil-shaped forms, and the erythroid marrow becomes increasingly ineffective. In patients with severe prolonged

iron-deficiency anemia, erythroid hyperplasia of the marrow develops, surpassing hypoproliferative. [19]

Diagnostic methods for investigating iron metabolism

Serum ferritin -The primary iron storage protein in the body, serum ferritin-ferritin also serves as a reserve of iron for the body. A spherical apoprotein shell that encapsulates a core of ferric hydroxyphosphate. The human ferritin molecule is composed of 24 subunits, of which there are two immunologically distinct types: H and L. Ferrous iron may enter (to interact with a ferroxidase centre on the ferritin H subunit) or exit the ferritin molecule via one of six channels that connect the interior cavity to the exterior of the molecule. In response to fluctuating levels of iron, macrophages secrete the protein known as serum ferritin. Other than iron, there are a number of factors that can affect ferritin synthesis. In healthy subjects, ferritin is the primary form of iron storage, and the concentration of ferritin in the serum is correlated with iron stores. Concentrations of serum ferritin that is lower than 15 g/L are indicative of iron depletion. Serum ferritin concentrations below 100 g/L may be associated with a lack of storage iron in patients who suffer from the anemia of chronic disease (ACD).Ferritin levels in the serum that is normal range from 15 to 300 g/L.

Transferrin and Transferrin Receptors-Transferrin is a single-chain polypeptide that can be found in plasma at concentrations ranging from 1.8 to 2.6 g/L as well as extra vascular fluid. It takes the plasma around 8–11 days to reach half life. The liver is the primary organ responsible for producing the protein. The process of its synthesis is inversely related to the amount of iron that is stored. Every molecule has the capacity to bind two atoms of ferric iron. Despite the fact that it only stores about 4 mg of body iron at any given time, it is essential to the transport of iron because more than 30 mg of iron passes through this compartment every day [20]. Both iron deficiency and erythroid hyperplasia are associated with an increase in TR levels. In ACD, the assay has been suggested as a useful indicator of the deficiency of body iron stores. This is due to the fact that ACD affects more women than men. Only when there is no storage iron present will the TRs in the serum rise to this level. The clinical validity of the test has not been established. [19]

Iron and Iron-Binding Capacity- In Serum the saturation of the total iron-binding capacity of transferrin (TIBC) provides a measurement of the amount of iron that is supplied to the tissues. In order to maintain normal erythropoiesis, a serum transferrin saturation of less than

15% is regarded as insufficient. An increase in total iron binding capacity (TIBC) is typical of iron deficiency. Inflammation typically results in a decreased serum iron concentration along with a normal or decreased TIBC. This is a characteristic response. [19]

Ferroportin- is a protein that contains a transmembrane domain and is essential for the release of iron from macrophages, the intestinal absorptive enterocyte, Hepatocyte, and placental syncytiotrophoblasts. Caeruloplasmin is necessary for the transport of Ferroportin to the cell surface, which is regulated by the hormone hepcidin.

Hepcidin - The expression of hepcidin goes up in response to elevated serum iron, iron overload, and inflammation. On the other hand, its expression goes down in response to iron deficiency, hypoxia, and increased erythropoietic activity. [21]

Iron deficiency anemia In India

In India, anemia affects approximately 57% of women and 25% of men between the ages of 15 and 49. Women are mildly anemic 26% of the time, moderately anemic 29% of the time, and severely anemic 3% of the time. Men are mildly anemic 20% of the time, moderately anemic 5% of the time, and severely anemic 0.4 percent of the time. Trends: The prevalence of anemia increased between the NFHS-4 and NFHS-5 surveys, rising from 53% in 2015-16 to 57% in 2019-21 among women and from 2[43.5 - 62.1] The average age of women who do not have children and who have been diagnosed with anemia is 53.1 [43.5 - 62.1].

Other causes of Anemia in Diabetes mellitus and their implications in diabetes mellitus

Non-nutritional causes or contributors to anemia include acute and chronic parasitic infestations or diseases (such as Malaria, Hookworm infestation, Schistosomiasis, HIV, Helicobacter Pylori Infection, Tuberculosis, and Cancer), genetic conditions (such as thalassemia and glucose-6-phosphate dehydrogenase [G6PD] deficiency and sickle cell trait), and environmental or support factors such as inadequate personal hygiene. Patients who are severely malnourished are at a greater risk of developing more severe forms of anemia. In marasmus, which occurs when patients are both protein- and calorie-deficient, the release of EPO is impaired in proportion to the reduction in metabolic rate.

Megaloblastic anemia is caused by a lack of vitamin B12 and folic acid, which inhibits DNA synthesis during the production of red blood cells. [22] The megaloblastic anemias are a group of disorders that are characterized by the presence of distinctive morphological appearances

of the developing red cells in the bone marrow. The marrow is usually hyper cellular, and the anemia is based on ineffective erythropoiesis.

Anemia of chronic inflammation and infection (AI) - One of the most common types of anemia seen in clinical settings is called anemia of acute and chronic inflammation and infection (AI). This type of anemia encompasses inflammation, infection, tissue injury, and conditions (such as cancer) associated with the release of proinflammatory cytokines. These alterations are the result of the actions of inflammatory cytokines and hepcidin, the key iron regulatory hormone, which took place at multiple stages of the erythropoiesis process .The severity of the hypoproliferative anemia, which is typically associated with progressive CKD and correlates with the stage of CKD, typically ranges from moderate to severe. Anemia is primarily caused by a failure of EPO production by the diseased kidney and a reduction in red cell survival. [23]

Anemia in different endocrinopathies-In men, the production of erythropoietin is stimulated by testosterone and anabolic steroids, but it is suppressed by castration and the administration of estrogen. Hypothyroid patients and those with pituitary hormone deficiencies, such as those with Addison's disease, are also at risk for developing mild anemia. Mild anemia is a common complication of hyperparathyroidism, and it could be caused by a decrease in EPO production as a result of the renal effects of hypercalcemia, or it could be caused by an impaired proliferation of erythroid progenitor cells.

Chronic liver disease -Patients who have chronic liver disease from nearly any cause may develop a mild form of hypoproliferative anemia at some point. Red cell survival is shortened, and production of erythropoietin (EPO) is insufficient to compensate for nutritional deficiencies caused by alcoholic liver disease and inadequate intake of food and nutrients. In addition, many diseases, conditions, and other factors can trigger the destruction of red blood cells within our bodies, which can result in hemolytic anemia. These causes can be inherited or acquired, but there are instances in which the underlying reason is unknown. Hemolytic anaemia has been linked to a variety of adverse health effects, including feelings of exhaustion and pain, irregular heartbeats, and even heart failure. [24]

Incidence of Anemia in Patients Diagnosed with Diabetes (Cases) and Healthy Subjects (Controls), Broken Down By Gender [25]

Cases	Anemic (%)	Non-Anemic (%)
Male	13 (86.7)	2 (13.3)
Female	29 (82.9)	6 (17.1)
Controls		
Male	1 (7.1)	13 (92.9)
Female	7 (19.4)	29 (80.6)

According to the findings of the Framingham Heart Study, people with diabetes have a significantly higher risk of developing coronary heart disease, peripheral artery disease, myocardial infarction, and congestive heart failure (an increase of one to five times, respectively).Patients diagnosed with diabetes mellitus often suffer from anemia as a result of co-occurring infections such as HIV, hookworm, and tuberculosis. The findings of a study carried out by Rossing and colleagues showed that there was a statistically significant connection between a lower Hb concentration and a decrease in glomerular filtration rate (GFR). [26]

Anemia is a risk factor for additional complications in diabetic patients, including cardiovascular disease as well as increased morbidity and mortality. Anemic diabetic patients are also more likely to develop left ventricular hypertrophy, which can lead to full-blown cardiovascular disease as well as chronic renal disease.

In individuals who are otherwise healthy, the symptoms of anemia include, but are not limited to, cognitive dysfunction, weakness, fatigue, and headache, shortness of breath, emotional instability, depression, and restless leg syndrome. [27]] This may make diabetic neuropathy even more difficult to treat and worsen the patients' quality of life. Optic atrophy and cerebral symptoms including dementia, depression, psychotic symptoms, and cognitive impairment may be prominent in cobalamin deficiency. [23]

It is estimated that thirty percent of people who have type 2 diabetes also have anemia. [28] Anemia is a co morbidity of both coronary heart disease and diabetes, and it affects at least one hundred seventy million people. It has been shown that anemia in these populations is associated with a highly significant increase in the likelihood of morbidity, mortality, and hospitalizations [29, 30, 31].

There is a correlation between anemia as co morbidity in patients with infectious diseases and an increased risk of mortality. [32, 33] Infections, skin changes, hearing loss, and an increased risk of dementia and impaired cognitive function are some of the nonvascular complications that can result from diabetes. Diabetes patients have a higher risk of infection and a more severe form of the disease. Incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia, in addition to decreased vascularization, are the reasons for this phenomenon. A wide variety of organisms can more easily colonise and thrive in hyperglycemic environments. Many common infections are seen in the diabetic population at a higher frequency and severity, whereas several rare infections are seen almost exclusively in the diabetic population. In the diabetic population, pneumonia, urinary tract infections, and skin and soft tissue infections are all more prevalent. [23]

Acute, chronic, and occult gastrointestinal bleeding is frequently exacerbated by the use of anticoagulant and anti platelet medications, and it is associated with increased mortality and morbidity [34, 36], as well as persistent anemia and iron deficiency [35]. Long-standing types 1 and 2 diabetes may affect the motility and function of the GI and genitourinary systems. The most obvious signs of gastrointestinal disease are a sluggish emptying of the stomach (also known as gastro paresis) and changes in the motility of both the small and the large intestine. [23]

In cases of megaloblastic anemia caused by a lack of cobalamin, the patient will typically exhibit symptoms such as paresthesias, muscle weakness, or difficulty walking; however, they may on occasion exhibit symptoms such as dementia, psychotic disturbances, or visual impairment. When positive Romberg and Lhermitte signs are present, it is common for patients to experience a loss of proprioception and vibration sensation. Ataxic gait may be present with spasticity. A dysfunction of the autonomic nervous system can lead to postural hypotension, as well as impotence and incontinence. [23] This will further complicate the neuropathy caused by diabetes.

Glycated hemoglobin and Iron deficiency anemia

In Iron deficiency anemia , there is decreased erythrocyte turnover rate, decreased formation of new hemoglobin molecules and a significant proportion of old glycated haemoglobin is present at a given point of time. Reduced iron stores have been linked to increase glycation of HbA1c. Diabetes may cause anemia through reducing absorption of iron, gastrointestinal bleeding and diabetic complications that cause anemia. [36] [37] [38] In chronic iron deficiency anemia, erythrocyte survival is prolonged there is a chronic hypoxia and hemoglobin (Hb) cannot be synthesized sufficiently due to iron deficiency. Therefore nonenzymatic glycosylation is affected and HbA1c percentage increases. [39] Another speculation that iron deficiency disrupts the quaternary structure of Hb, and that this structure causes the glucose to bind more easily to the β globulin chain [40]

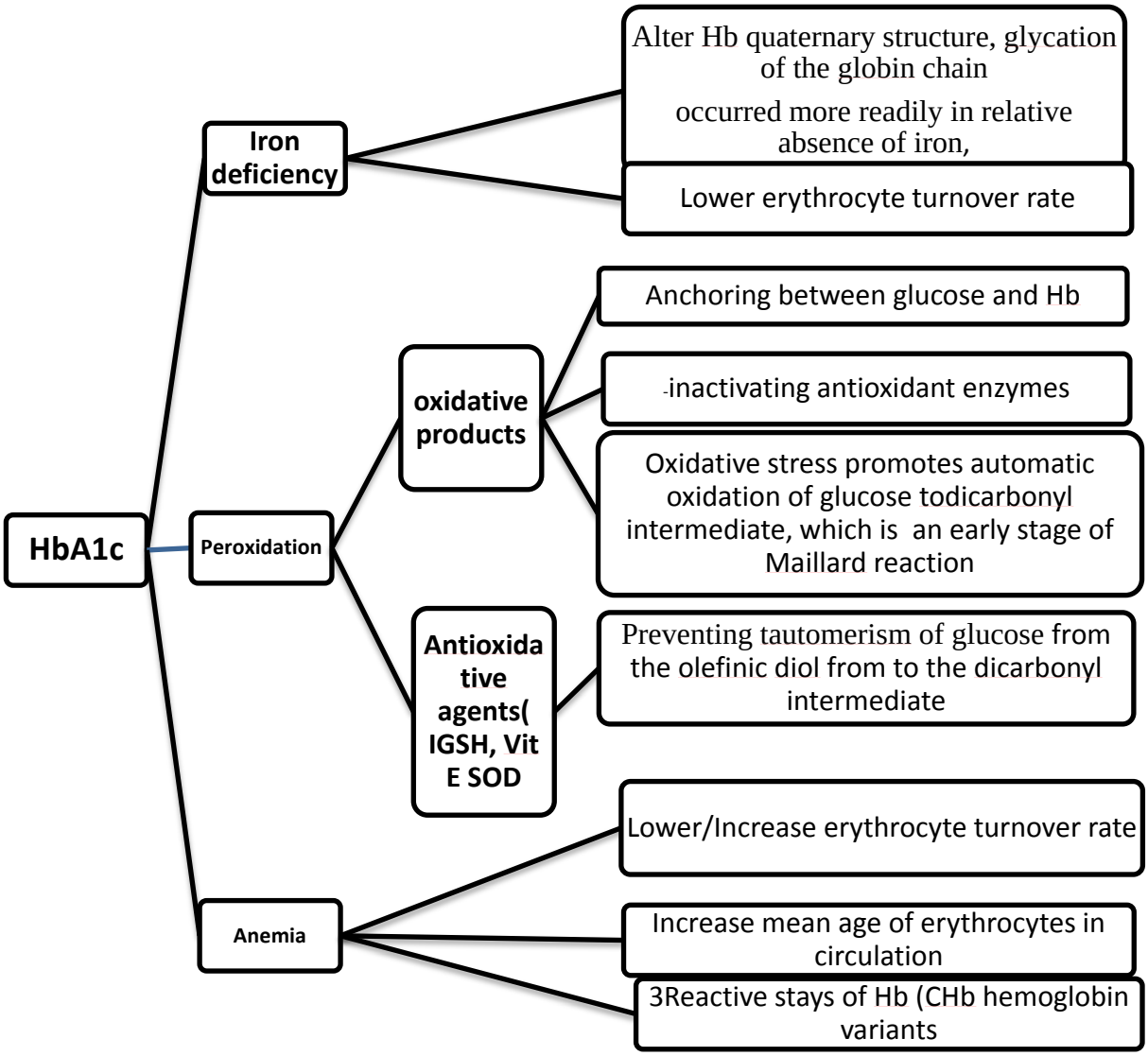
HbA1c
Iron deficiency
Alter Hb quaternary structure, glycation of the globin chain
occurred more readily in relative absence of iron,
Lower erythrocyte turnover rate
Peroxidation
oxidative products
Anchoring between glucose and Hb
-inactivating antioxidant enzymes
Oxidative stress promotes automatic oxidation of glucose todicarbonyl intermediate, which is an early stage of Maillard reaction
Antioxidative agents(IGSH, Vit E SOD
Preventing tautomerism of glucose from the olefinic diol from to the dicarbonyl intermediate
Anemia
Lower/Increase erythrocyte turnover rate
Increase mean age of erythrocytes in circulation
3Reactive stays of Hb (CHb hemoglobin variants

Figure1 -Depicting effect of iron deficiency anemia on HbA1c

Studies evaluating effect of Iron deficiency anemia on HbA1c in Diabetes Mellitus

Juliana Frezza Silva et al conducted a study on total of 122 non diabetic subjects and divided them into 2 groups out of which 61 patients with iron deficiency and 61 patients without iron deficiency. HbA1c was measured and compared between the two groups and the results of HbA1c showed significant difference between the patients diagnosed with iron deficiency anemia [HPLC 5.6 ± 0.4% (38 ± 4.4 mmol/mol) and IT 5.7 ± 0.4% (39 ± 4.4 mmol/mol)]. Whereas the patient without anemia showed a result of anemia [HPLC 5.3 ± 0.4% (34 ± 4.4 mmol/mol) and IT 5.3 ± 0.3% (34 ± 3.3 mmol/mol)]. According to the author Total haemoglobin (Hb), haematocrit, mean corpuscular volume (MCV), and ferritin all had s ignificant negative associations with HbA1c values determined by IT (r = 0.557; r = 0.539; r = 0.488; r = 0.499; p b 0.01; respectively). These negative relationships were weaker with HP LCmeasured HbA1c (r = 0.272; r = 0.250; r = 0.273; r = 0.229 for Hb, haematocrit, MCV, an d ferritin, respectively p =0.05 respectively.[41]

Faisal Alsayegh et al conducted a study on total of 1580 diabetic patients which showed that diabetic females have higher rates of anemia when compared to males (35.8% vs. 21.3% respectively, $p < 0.001$) however there was no statiscally significant correlation between HbA1c and anemia in both sexes with $p < 0.001$[42]

Rahul Purbey et al conducted a study on 100 patients where 50 non diabetic IDA patients were taken as cases and 50 non diabetics non anemic were taken as controls which showed that anemic patients had significantly higher fasting and random blood sugars and having more number of subjects in Prediabetic range based on HbA1c values Non-diabetic IDA patients had considerably higher HbA1c levels (p-value 0.05), but HbA1c levels fell significantly (p 0.0001) after 3 months of anemia treatment. As a result, it was found that iron deficiency anemia has an inverse relationship with HbA1c levels.

Akanksha Preety et al conducted a study on 80 subjects in which 60 were taken as cases and 20 were age and sex matched
controls.The study demonstrated that HbA1c was statistically significantly higher in patients with iron deficiency anaemia than in healthy controls, with a pvalue of less than 0.001, and it dropped after iron treatment, demonstrating a statistically significant correlation. He also postulated that among patient with iron deficiency anemia there was a statistically significant correlation between hemoglobin and HbA1c with p value equal to 0.005.

Vishal kalasker et al 2014 study on the impact of iron deficiency anemia on glycosylated hemoglobin levels in Indian adults without diabetes
proposed that Hb concentrations are favourably corrected by HbA1c concentration and that th ere is an association between HbA1c concentration and iron deficiency anaemia. But they det ermined that iron deficiency anaemia is unlikely to be a serious concern when diagnosing dia betes using HbA1c level as per American Diabetes Association (ADA) recommendations. [43]

In contrast, iron deficiency anaemia raises HbA1c levels in diabetic people with regulated plasma glucose levels, according to a study by **Alap L. Christy et al**. They proposed that ele vated HbA1c values are positively correlated with iron deficient anemia. [44]

Lavanya Rajagopal et al conducted a study which included 150 Controlled diabetics (75 with IDA and 75 without IDA) and 150 non-diabetics which showed that mean HbA1c was higher in controlled diabetic patients with and without IDA. The difference in anemia was also statistically significant between the two groups. [45]

S.V. Madhu et colleagues. conducted research on 122 participants, including 62 IDA cases and 62 healthy controls who were matched for sex and age which revealed that IDA had higher HbA1c levels than healthy controls.(p-value = 0.001). Additionally, they discovered that there was a strong negative association between HbA1c and hemoglobin (r=-0.632), hematocrit (r=-0.652), RBC count (r=-0.384), and ferritin (r=-0.441). Iron supplementation over a period of time caused HbA1c to return to normal range and came to the conclusion that before diagnosing diabetes and pre-diabetes based on HbA1c, iron deficiency should be treated. [46]

A cross-sectional study on 174 diabetic individuals, including 87 patients with IDA and 87 without IDA, was undertaken by **Absra Solomon Aida et al.** In the IDA group, they observed that mean hemoglobin, mean corpuscular volume, and mean cell hemoglobin concentration were all lower than in the non-IDA group. They concluded that HbA1c is much lower in diabetic patients who have IDA compared to those who do not.[47]

Anemic patients of iron deficiency anemia had significantly lower HbA1c levels than the control group with a p value of less than 0.05**. Nitin Sinha et al.** found that these levels rose after treatment with a statistically significant p value below 0.01.[48]

Ensieh nasli-esfahani et al in their study on 90 patients with type 2 diabetes mellitus which were divided into 45 who received iron supplementation for 3 months and 45 in the control

group and it showed that Hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, serum iron, ferritin, total iron-binding capacity, and HbA1c were significantly improved in the intervention group in comparison with the control group with P = 0.005. And hence concluded that iron replacement can decrease HbA1c in anemic patients with IDA and type 2 diabetes mellitus. [49]

SM Attard et al conducted a study in which they analyzed 7308 adults aged 18-75 years in which they found out that approximately 65% of individuals with diabetes in our sample were concordantly classified with diabetes using both FBG and HbA1c, while 35% had a discordant diabetes classification: they were classified using either FBG or HbA1c, but not both. And concluded that classifying diabetes solely on the basis of HbA1c in anemia/ID endemic area is misleading and it leads to under diagnosis of diabetes in women and over diagnosis in men. [50]

Eloísa Urrechaga et al conducted a study on 661 patients in which there were 336 females (228 menopausal and 108 premenopausal) and 325 males (237 age> 50 years and 88 age < 50 years). Which showed that All groups presented increasing HbA1c values in parallel with iron deficiency, subclinical and anemia, but the level of significance was not homogeneous in the different groups and concluded that there was a positive correlation between iron deficiency and increased HA1c levels. In diabetic patients with IDA should be interpreted with caution, due to the possibility of spurious increment in HbA1c. [51]

According to **Emma English et al** research which included 12 relevant articles from 1990 to 2014, HbA1c is likely to be affected by iron deficiency and IDA, which can lead to a spurious increase in HbA1c values. On the other hand, non-IDA may lead to a decreased HbA1c value.[52]

Earl S. Ford et al cross-sectional analysis of 8296 persons over the age of 20 revealed a substantial positive connection between hemoglobin and HbA1c. They reported that subjects with and without iron deficiency had respective mean HBA1c concentrations of 5.56% and 5.46% (P = 0.095). And came to the conclusion that since changes in erythrocyte turnover could affect the test result, caution should be exercised when diagnosing diabetes and prediabetes in persons with high or low hemoglobin when the HbA1c level is close to 6.5% or 5.7%, respectively.[53]

Merlin c. thomas et al conducted a study in which 190 patients accounting for 23 % of total had unrecognized anemia which was two to three times higher for patients with matched renal impairment and iron stores in general population. There was statistically significant correlation between hemoglobin and transferrin saturation, glomerular filtration rate, sex, hba1c with p value less than 0.0001 in all and concluded that anemia accompanies diabetes in majority particularly in those with diabetic nephropathy. [54]

MATERIAL AND METHODS

Study Place: The study was conducted in Department of Medicine, Santosh Medical College and hospital, Ghaziabad

Study frame: Study was conducted in Diabetes mellitus patients who attended the Medicine OPD of Santosh Hospital.

Study Design**: Cross Sectional Study**

In this study, as we want to observe and analyze iron deficiency anemia in diabetes mellitus and its effect on hba1c. Therefore in order to calculate the sample size, we need to have the estimated prevalence of type 2 diabetes mellitus as well as the prevalence of iron deficiency anemia in type 2 diabetes mellitus patients. To this reference, we have found that past researches have reported the prevalence of type 2 diabetes in India within a range of 1.9% to 25.2%. For the sample size calculation, we will take upper limit of this range (i.e. 25.2%). Also, a research work suggested that the prevalence of iron deficiency anemia in type 2 diabetes patients was 67%. On calculating the sample size using these values and the sample size formula with the correction factor by Fleiss given below:

$$n_1 = \frac{\left[\left(Z_{\frac{\alpha}{2}}\sqrt{(r+1)\bar{p}\bar{q}} + Z_{1-\beta}\sqrt{(rp_1q_1 + p_2q_2)}\right)\right]}{r(p_1 - p_2)^2}$$

$$\text{And } n_2 = rn_1$$

Where

n_1= number of exposed

n_2= number of unexposed

$Z_{\frac{\alpha}{2}}$= standard normal deviate for two-tailed test based on alpha level (relates to the confidence interval level)

$Z_{1-\beta}$=standard normal deviate for one-tailed test based on beta level (relates to the power level)

r= = ratio of unexposed to exposed

p_1= proportion of exposed with disease and $q_1 = 1 - p_1$

p_2= proportion of unexposed with disease and $q_2 = 1 - p_2$

$\bar{p} = \frac{p_1 + r p_2}{r+1}$ And $\bar{q} = 1 - \bar{p}$

For the Fleiss method with the correction factor, take the sample size from the uncorrected sample size formula and place into the following formula:

$$n_{1cc} = \frac{n_1}{4}\left[1 + \sqrt{1 + \frac{2(r+1)}{n_1 r |p_2 - p_1|}}\right]$$

Taking the sample size evaluated from Fleiss with CC formula and adjusting it for loss to follow up as 20%, we get the final sample size as 64 patients. Results from OpenEpi, Version 3, open source calculator—SS Cohort

Sample Size : X-Sectional, Cohort, & Randomized Clinical Trials			
Two-sided significance level(1-alpha):			95
Power(1-beta, % chance of detecting):			80
Ratio of sample size, Unexposed/Exposed:			1
Percent of Unexposed with Outcome:			25
Percent of Exposed with Outcome:			69
Odds Ratio:			6.5
Risk/Prevalence Ratio:			2.7
Risk/Prevalence difference:			44
	Kelsey	**Fleiss**	**Fleiss with CC**
Sample Size – Exposed	23	22	26
Sample Size-Nonexposed	23	22	26
Total sample size:	46	44	52

References:

1. SachinAtre, Sona Deshmukh, Manjusha Kulkarni , Prevalence of type 2 diabetes mellitus (T2DM) in India: A systematic review (1994–2018),Diabetes & Metabolic Syndrome: Clinical Research & Reviews ,Volume 14, Issue 5,2020,Pages 897-906,ISSN 1871-4021.

2. Panda AK, Ambade RA. Prevalence of anemia and its correlation with HBA1c of patients in Type-II diabetes mellitus: A pilot study. Natl J Physiol Pharm Pharmacol 2018;8(10):1409-14

Methodology

- HbA1c – measured by direct method
- FBS and PPBS – measured by glucose oxidase - peroxidase method
- Ferritin- Fully automated bidirectional infrared chemiluminescent immune assay
- % Transferrin saturation –derived Fe^{2+} and TIBC value
- Iron- Ferrozine method without deproteinisation
- TIBC- Spectrophotometeric assay

Inclusion criteria-

Criteria for the diagnosis of diabetes as per the American Diabetic Association are :

- HbA1C more than or equal to 6.5%
- Fasting Plasma Glucose equal to or above 126 mg/dL.
- 2-hrs plasma glucose ranging 200 mg/dL or above during an Oral Glucose Tolerance Test.
- Random plasma glucose ranging 200 mg/dL or above where random is defined as blood glucose without regard to time since the last meal

Exclusion criteria –

- Failure to obtain informed consent
- Chronically sick patient
- Type 1 DM

Ethical issues:

- Informed written consent will be taken from all the participants.
- Data will be kept confidential.
- Due clearance shall be obtained from the ethical committee beforehand.
- Patients will be offered adequate treatment at all levels for type 2 diabetes and co morbidities.

Data management and Statistical analysis

The data will be collected and entered in MS excel 2010. Different statistical analysis will be performed using R software version 4.0.2. The one-sample Kolmogorov – Smirnov test will be employed to determine whether the data sets differed from a normal distribution or not. Normally distributed data will be analyzed using parametric tests and non - normally distributed data will be analyzed using non parametric tests. Descriptive statistics will be calculated for qualitative and categorical variables. Graphical representation of the variable will be shown to understand the results clearly and to measure the association for categorical dataset will be analysed using Chi-Square test. Independent T-test or student t-test will be applied to measure the mean difference between two groups. Correlation will be estimated to measure the strength of relationship between two or more quantitative variables

Results and Observations

Out of 56 patients, 32 were diagnosed as anemic (hb<12 and<13 for females and males, respectively, with a mean of 53), whereas 24 had normal hemoglobin. Participants' mean age was 51.51 years old. Mean Hb, Hba1c, serum iron levels, serum ferritin, and eGFR in our study population were 11.725, 9.166, 66.91, 291.003, and 67.321, respectively. In our study, it was found that 57% of patients had anemia, out of which 62% were normocytic normochromic and 38% were microcytic hypochromic; non-anemic cases were found to be 43%. The mean eGFR in patients with anemia was 63.13 +/-18.407, and non-anemic was 72.92+/-17.849. The relationship between Hba1c and Hb values was negative (p = 0.09). Likewise, the relationship between S. iron levels and Hb values was a negative correlation (p = 0.87). There was a moderate positive correlation (p = 0.05) between S. EGFR (MDRD) and Hb Values. The relationship between Hb and iron profile was/had a positive correlation (p = 0.00). No significant statistical correlation was found between eGFR and type of anemia (p=0.293), which in our case was microcytic hypochromic and normocytic normochromic anemia.

Anemic(Anemia, 1= Yes, 2= No) N=32			
	Mean	**Std. Deviation**	**Std. Error of Mean**
Age/Sex	54.44	12.799	2.262
HB	10.444	1.5727	0.2780
MCV	83.1569	6.88967	1.21793
RBS	204.44	74.021	13.085
HbA1C	8.7041	2.05415	0.36313
Retic Count	1.228	0.3761	0.0665
S. Iron Levels	67.969	70.9732	12.5464
TIBC	345.806	56.8787	10.0548
transferrin saturation	21.1428	18.40736	3.25399
S. Ferritin	258.5431	232.51728	41.10364
Blood Urea	31.53	13.739	2.429
Serum Creatinine	1.0497	0.29319	0.05183
EGFR MDRD	63.13	18.407	3.254

Table1 Depicting Descriptive statistics for clinical variables of the Anemic patients

Non Anemic(Anemia, 1= Yes, 2= No) N=24			
	Mean	**Std. Deviation**	**Std. Error of Mean**
Age/Sex	47.63	8.412	1.717
HB	13.433	1.1224	0.2291
MCV	83.4308	5.08105	1.03716
RBS	239.92	97.749	19.953
HbA1C	9.7838	2.68799	0.54868
Retic Count	1.392	0.3296	0.0673
S. Iron Levels	65.504	27.6863	5.6514
TIBC	338.575	76.9642	15.7103
transferrin saturation	28.8504	50.31829	10.27118
S. Ferritin	334.2833	395.93611	80.82012
Blood Urea	26.79	11.112	2.268
Serum Creatinine	1.0138	0.40927	0.08354
EGFR MDRD	72.92	17.849	3.643

Table2 Depicting Descriptive statistics for clinical variables of the non Anemic patients

Total (Anemic and non anemic) N=56			
	Mean	**Std. Deviation**	**Std. Error of Mean**
Age/Sex	51.52	11.554	1.544
HB	11.725	2.0370	0.2722
MCV	83.2743	6.12938	0.81907
RBS	219.64	86.010	11.494
HbA1C	9.1668	2.38547	0.31877
Retic Count	1.298	0.3631	0.0485
S. Iron Levels	66.913	56.2246	7.5133
TIBC	342.707	65.6780	8.7766
transferrin saturation	24.4461	35.56118	4.75206
S. Ferritin	291.0032	312.18497	41.71747
Blood Urea	29.50	12.792	1.709
Serum Creatinine	1.0343	0.34470	0.04606
EGFR MDRD	67.32	18.658	2.493

Table3 Depicting Descriptive statistics for clinical variables of the total patients

ANOVA Table						
		Sum of Squares	**Df**	**Mean Square**	**F**	**Sig.**
Age/Sex * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	636.482	1	636.482	5.126	0.028
	Within Groups	6705.500	54	124.176		
	Total	7341.982	55			
HB * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	122.573	1	122.573	62.648	0.000
	Within Groups	105.652	54	1.957		
	Total	228.225	55			
MCV * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	1.029	1	1.029	0.027	0.870
	Within Groups	2065.285	54	38.246		
	Total	2066.314	55			
RBS * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	17263.149	1	17263.149	2.393	0.128
	Within Groups	389611.708	54	7215.032		
	Total	406874.857	55			
HbA1C * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	15.987	1	15.987	2.907	0.094
	Within Groups	296.988	54	5.500		
	Total	312.975	55			
Retic Count * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	0.367	1	0.367	2.878	0.096
	Within Groups	6.883	54	0.127		
	Total	7.250	55			
S. Iron Levels * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	83.303	1	83.303	0.026	0.873
	Within Groups	173783.138	54	3218.206		
	Total	173866.441	55			
TIBC * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	717.133	1	717.133	0.164	0.687
	Within Groups	236530.984	54	4380.203		
	Total	237248.117	55			
transferrin saturation * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	814.727	1	814.727	0.640	0.427
	Within Groups	68738.142	54	1272.929		
	Total	69552.869	55			
S. Ferritin * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	78673.086	1	78673.086	0.804	0.374
	Within Groups	5281596.998	54	97807.352		
	Total	5360270.084	55			
Blood	**Between Groups**	308.073	1	308.073	1.914	0.172

Urea * Anemia, 1= Yes, 2= No	**(Combined)**					
	Within Groups	8691.927	54	160.962		
	Total	9000.000	55			
Serum Creatinine * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	0.018	1	0.018	0.147	0.703
	Within Groups	6.517	54	0.121		
	Total	6.535	55			
EGFR MDRD * Anemia, 1= Yes, 2= No	**Between Groups (Combined)**	1314.881	1	1314.881	3.982	0.051
	Within Groups	17831.333	54	330.210		
	Total	19146.214	55			

Table 4 Depicting Descriptive statistics for clinical variables of the study subjects

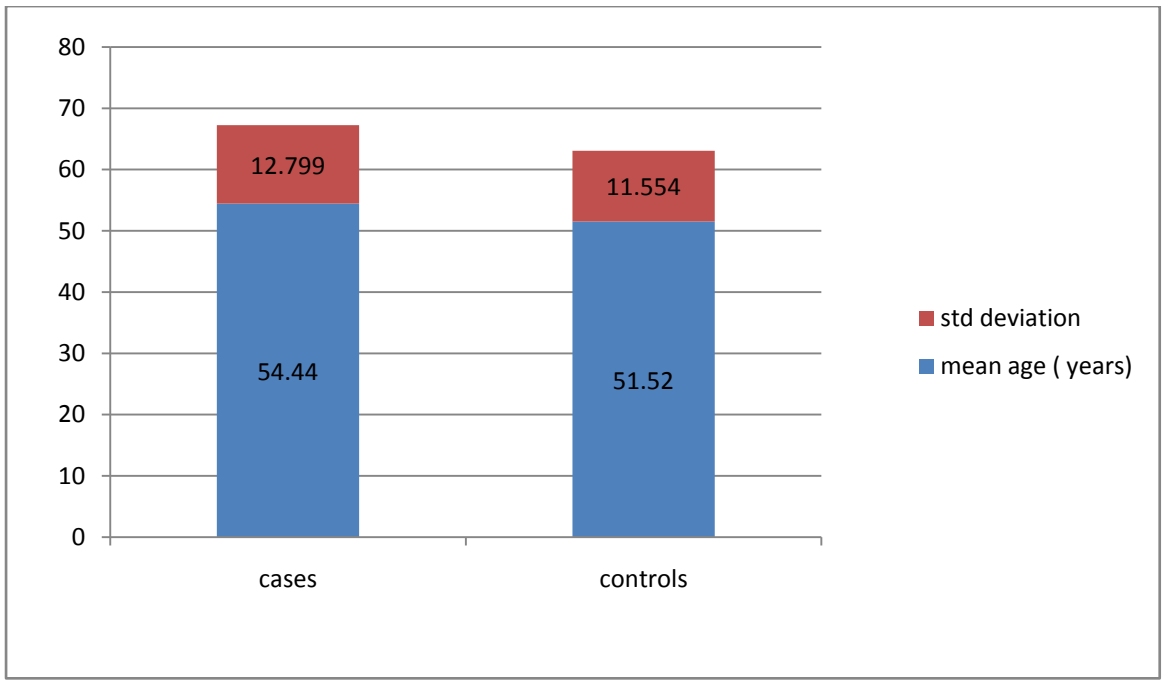

Figure2. Depicting mean age of case and control subjects

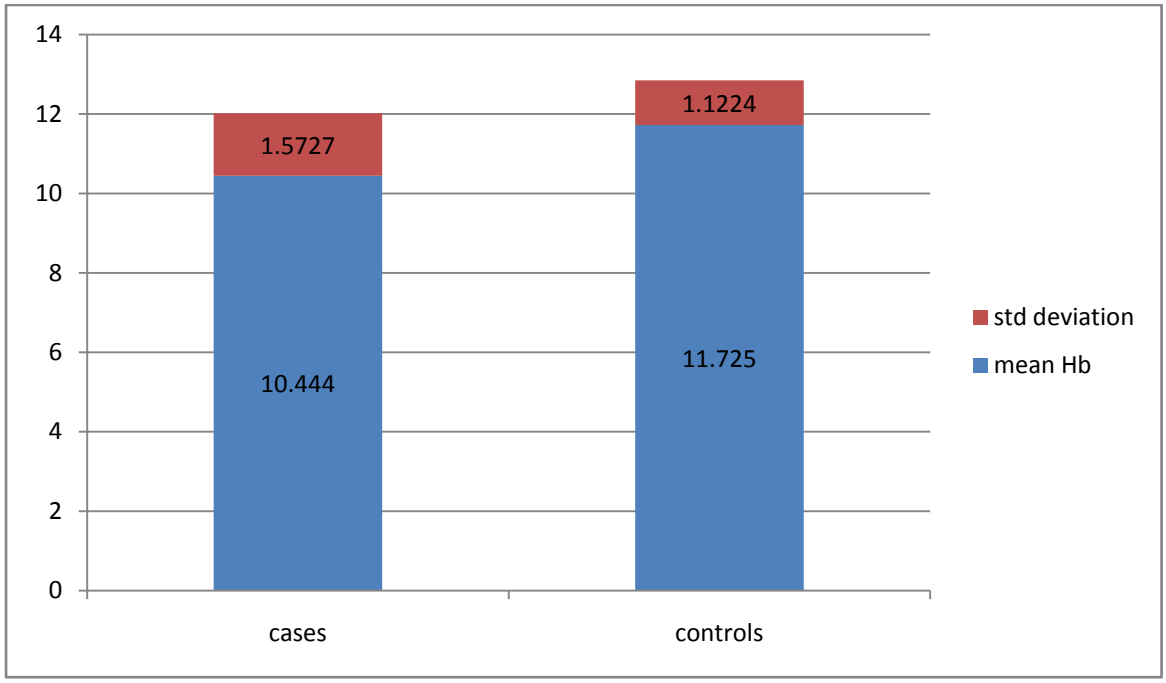

Figure 3. Depicting mean Hemoglobin among case and control subjects

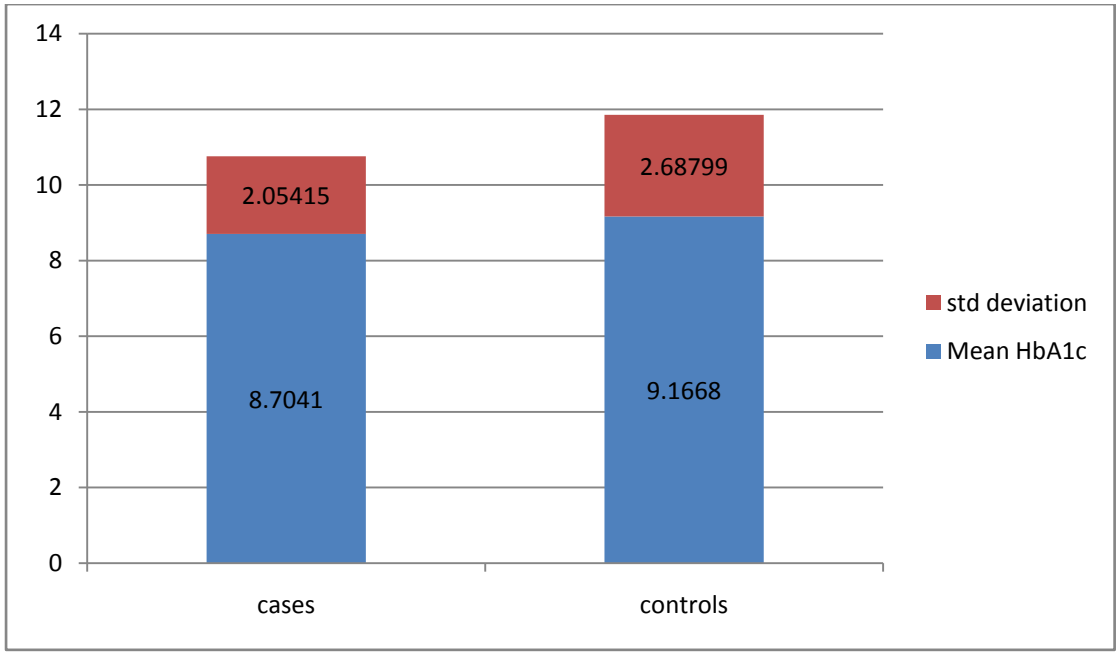

Figure 4. Depicting mean HbA1c among case and control subjects

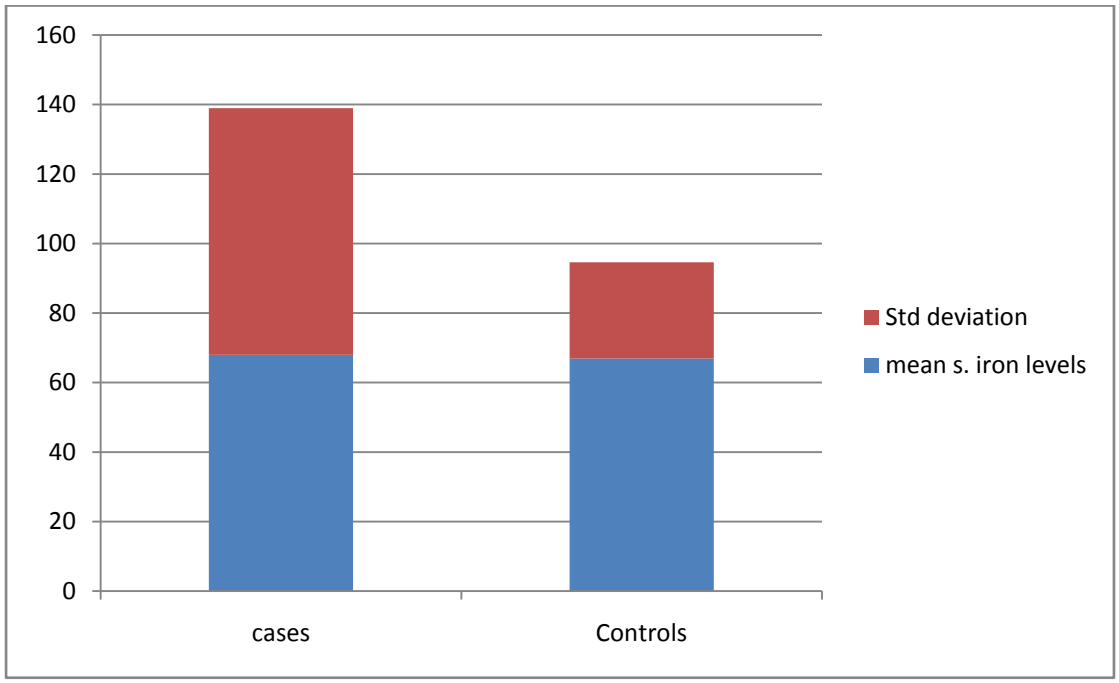

Figure 5. Depicting mean s. iron levels among anemic and non-anemic

Discussion

The HbA1c fraction of hemoglobin A1 is by far the most common form of this protein. During the glycation process, glucose in the red cells reacts with the N-terminal valine amino acid of both the beta chains to generate an aldimine linkage. This linkage is essential for the glycation process. This link is then reorganized to create a ketamine link, which is a more stable. Not only is it considered to be the primary objective of glycemic control, but it is also utilised as a diagnostic criterion in the guidelines that have been established by the American Diabetes Association. In the beginning, individuals believed that glucose levels were the sole factor that may influence HbA1c. On the other hand, a number of studies have shown that it is raised in conditions that are not related to diabetes. These conditions include hemoglobinopathies, chronic kidney illnesses, pregnancy, and nutritional anemias. One of the most prevalent forms of nutritional anemia that may be discovered in India is that which is brought on by a deficiency of iron. However, the results of our research demonstrated that there is no statistically significant link between HbA1c and anemia.. Similar to our study, **Faisal Alsayegh et al.** conducted a study that showed no statistically significant correlation between HbA1c and anemia in both sexes with p 0.001.

variables	Mean	Std. Deviation	Pearson Correlation	Sig. (2-tailed)/ p value
HbA1C (n=56)	9.18	2.405	1	.426
HB(n=56)	11.73	2.067	.109	
HbA1C(n=56)	9.18	2.405	1	.125
Anemia1Yes 2 No(n=56)	1.43	.499	.208	
HbA1C(n=56)	9.18	2.405	1	.167
S.IronLevels9n=56)	66.91	56.173	-.187	
HbA1C(n=56)	9.18	2.405	1	0.208
S. Ferritin	290.96	312.218	.171	

Table 5 Depicting Correlation Between Hba1c And Hb, HbA1c and anemia, HbA1c and iron levels, HbA1c and serum ferritin

The HbA1c levels of 120 diabetics, 70 of whom were women and 50 of whom were men, were compared with those of the same number of iron-sufficient, non-anemic individuals, and the researchers came to the conclusion that iron deficiency anaemia raises HbA1c levels in

diabetics with controlled plasma glucose levels. The study was carried out by **Alap L.** Christy et al. Elevation was more in women (7.02 1.58%). No significant correlation was found between HbA1c and ferritin or haemoglobin.

In contrast to the findings of our investigation, **Rahul Purbey and his colleagues** conducted a comparison study that lasted for one and a half years. They employed fifty non-diabetic patients with IDA as their cases, and fifty non-diabetic patients without anaemia as their controls. At the beginning, their iron profiles and HbA1c levels were tested and compared, and the results showed that there was a positive correlation that was statistically significant. After three months of treatment for anaemia, non-diabetic IDA patients had considerably higher HbA1c levels (p-values less than 0.05), and HbA1c levels reduced significantly (p 0.0001) following the treatment.

Akanksha Preety et al. in their prospective interventional study done on patients with iron deficiency anemia based on WHO criteria cut-off point and age, sex-matched control patients, showed that HbA1c was significantly higher in patients with iron deficiency anaemia (mean HbA1c 7.12 0.608) than healthy controls(mean HbA1c 5.85 0.681) with p-value 0.001, which decreased(with mean HbA1c6.32 0.681%) following iron treatment, showing a statistically significant correlation with a p-value less than 0.001. Among patients with iron deficiency anemia, haemoglobin and HbA1c showed a negative correlation (r = -0.26), which was statistically very significant (p = 0.005).

A study that was conducted in 2014 by **Vishal Kalasker et al** revealed a favourable association between HbA1c and Hb that was statistically significant. As a result, they are of the opinion that HbA1c concentrations serve to positively rectify Hb concentrations.

Lavanya Rajagopal et al. found a statistically significant positive correlation between HbA1c and anaemia with a p-value less than 0.05 in their cross-sectional study of 150 controlled diabetics (75 with IDA and 75 without IDA) and 150 non-diabetics (75 with IDA and 75 without IDA) in which HbA1C, complete hemogram, iron profile, and FPG were tested**.** The mean HbA1C in controlled diabetics with and without IDA was 8.810.13 & 5.790.01, respectively (P 0.05), and in non-diabetics with and without IDA was 6.840.07 & 5.120.04, respectively (P 0.05). Both diabetics and people without diabetes had statistically significant (p 0.05) differences between having no, mild, moderate, or severe anemia. The mean HbA1C% was highest in groups with severe anemia.

In their study of 62 iron deficient individuals and 60 healthy controls, **S.V. Madhu and colleagues** found a significant negative correlation between HbA1c and haemoglobin with a correlation coefficient of -0.632, HbA1c and hematocrit with a correlation coefficient of -

0.652, HbA1c and RBC count with a correlation coefficient of -0.384, and HbA1c and ferritin with a correlation coefficient of Additionally, the levels of HbA1c in those diagnosed with IDA dropped by a substantial amount (5.51 0.696 before treatment vs 5.044 0.603 after treatment; p 0.001).

Absra Solomon et al. found a statistically significant positive correlation between iron levels and haemoglobin, iron levels and mean corpuscular volume, iron levels and mean cell haemoglobin, and iron levels and mean cell haemoglobin concentration. The study was done on 174 diabetic patients, 87 with IDA and 87 without IDA**.** The HbA1c (%) level was significantly lower in the IDA group (6.18 1.57) compared with the non-IDA diabetic patients (7.74 1.81) (p 0.05).His study on 50 patients found a statistically significant positive correlation between HbA1c and iron levels with a p-value of less than 0.05, which increased following treatment with a statistically significant p-value of less than 0.01. In addition, there was a significant difference between the baseline values of patients and controls (0.29 g/dL vs 0.74 g/dL, P 0.01).

In his study conducted on ninety type 2 diabetes mellitus (T2DM) patients with IDA, the intervention group (n = 45) received 200 mg/day oral iron for 3 months, and the control group (n = 45) received an oral placebo for the same period. The correlation between iron levels and haemoglobin, iron levels and mean corpuscular volume, iron levels and mean corpuscular haemoglobin, and iron levels and HbA1c was statistically significant at P 0.005.

After taking into account factors such as age, gender, and racial or ethnic background, **Earl S. Ford and colleagues** found a positive association between haemoglobin and HbA1c that was statistically significant. In addition to this, they found that the mean concentrations of HbA1c were 5.56% among people who had iron insufficiency and 5.46% among participants who did not have iron deficiency (P = 0.095).

Akanksha Preety et al. showed that among patients with iron deficiency anemia, haemoglobin and HbA1c showed a negative correlation (r =-0.26), which was statistically very significant (p = 0.005).

With a p-value that was lower than 0.0001**, Thomas et al.** demonstrated that there is a statistically significant association between haemoglobin and HbA1c. They came to the conclusion that anaemia is a common complication of diabetes, particularly among those who suffered from diabetic nephropathy.

Alap L. Christy et al. discovered a link between iron deficiency anemia and higher HbA1C levels, particularly in people with FPG ranging from 100 to 126 mg/dl compared to people with normal plasma glucose levels (100 mg/dl**).** However, no significant correlation was

found. Hence, the author strictly felt the need to consider iron deficiency anemia before altering the treatment regimen for diabetic patients.
Table 5 shows that the Relationship between S. Iron Levels and Hb Values Was A Negative Correlation (p = 0.87).**Akanksha Preety et al.,** in their study, showed a statistically significant positive correlation between iron deficiency anaemia and HbA1c with a p-value equal to 0.005.

A study conducted in 2014 by **Vishal Kalasker et al.** showe**d** a statistically significant positive correlation between HbA1c and iron deficiency anemia, as HbA1c concentration tended to be lower in the presence of iron deficiency anemia.

When persons with diabetes and IDA were compared to healthy controls, the researchers from **S.V. Madhu and colleagues** found a statistically significant positive link between HbA1c and IDA. The p-value for this correlation was 0.001. **Akanksha Preety and colleagues** discovered a statistically significant correlation with a p-value of less than 0.001 when the mean HbA1c of patients with iron deficiency anaemia was higher than the mean HbA1c of the healthy control group (5.85+/-0.681). These patients had a mean HbA1c of 7.12+/-0.608, while the healthy control group had a mean HbA1c of 5.85+/-0.6 (significant). Patients suffering from iron deficiency anaemia had a mean HbA1c that dropped from 7.12+/-0.681% to 6.32+/-0.681% after receiving iron treatment. The p-value for this change was less than 0.001, indicating that it was statistically significant**..**
Alap L. Christy et al. compared 120 diabetics, 70 females and 50 males, with iron deficiency anemia and the same number of iron-sufficient non-anemic individuals, and they found that HbA1c levels were elevated (6.8+/- 1.4%) in iron-deficient individuals as compared to controls with controlled plasma glucose levels. In addition, women saw more significant height increases (7.02 vs 1.58%). They hypothesized a link between iron deficiency anemia and elevated HbA1c values. In his cross-sectional study of 174 diabetic patients, 87 with IDA and 87 without, he found that HbA1c and iron levels were linked in a way that was statistically significant. He did this by showing that the hba1c (%) level was significantly lower in the IDA group (6.18+/-1.57) than in the non-IDA diabetic patients (7.74+/-1.81) with p less than 0.05.
Elosa Urrechaga et al. conducted a study on 661 patients. A statistically significant positive correlation between iron levels and HbA1c was found in 336 females (228 menopausal and 108 premenopausal) and 325 males (237 aged > 50 years and 88 aged <50 years).

Our study shows no statistically significant correlation between HbA1c and serum ferritin with a p value> 0.005Likewise, **Alap L. Christy et al.** showed no statistically significant correlation between HbA1c and ferritin or haemoglobin.

Our study shows a statistically significant relationship between gender and Hb values with a positive correlation (p = 0.03).In a similar vein, **Merlin C. Thomas and colleagues** demonstrated that there was a statistically significant correlation between haemoglobin and sex with a p-value that was less than 0.0001 across the board. They came to the conclusion that anemia is a common complication of diabetes, particularly in patients who suffered from diabetic nephropathy.

	Anemia , N=32		**Non. Anemia, n=24**		
	Mean	**Std. Deviation**	**P value**	**Std. Deviation**	**P value**
Age/Sex	54.44	12.80	0.03	8.41	0.03
HB	10.44	1.57	0.00	1.12	0.00
MCV	83.16	6.89	0.87	5.08	0.87
RBS	204.44	74.02	0.13	97.75	0.13
HbA1C	8.70	2.05	0.09	2.69	0.09
Retic Count	1.23	0.38	0.10	0.33	0.10
S. Iron Levels	67.97	70.97	0.87	27.69	0.87
TIBC	345.81	56.88	0.69	76.96	0.69
transferrin saturation	21.14	18.41	0.43	50.32	0.43
S. Ferritin	258.54	232.52	0.37	395.94	0.37
Blood Urea	31.53	13.74	0.17	11.11	0.17
Serum Creatinine	1.05	0.29	0.70	0.41	0.70
EGFR (MDRD)	63.13	18.41	0.05	17.85	

Table 6 Descriptive statistics for clinical variables of the study subjects

Variables	Mean	Std. Deviation	P value
Anemia, 1= Yes, 2= No	63.13	18.407	.050
eGFR MDRD	72.92	17.849	

Table 7 Depicting statistically significant correlation between anemia and eGFR

Our study showed a significant correlation between eGFR and anemia.

The study on the prevalence of anemia in diabetic adult outpatients in Northeast Ethiopia conducted by **Temesgen Fiseha et al** in 2019 concluded that the prevalence of anemia increased with stage of CKD, from 22.6% at stage 1 to 100% at stage 4.

Thomas et al. showed that there was a statistically significant correlation between haemoglobin and glomerular filtration rate with a p-value less than 0.0001 in all and concluded that anemia accompanies diabetes in the majority, particularly in those with diabetic nephropathy.

Women with T2DM are more likely to develop kidney difficulties due to poor metabolic regulation, according to a 2016 study by **Ayami Kajiwara et al.**

Conclusion

The results of our research indicate that diabetes patients with iron-deficient anemia do not have any changes to their HbA1c. Thus, HbA1c may be used in making treatment decisions for diabetes mellitus even when iron deficiency anemia is present. Given how common IDA is in India, our study suggests that measuring iron, Hb, and HbA1C simultaneously may be optional to get a good idea of glycemic status. Some studies have found that people with IDA have much higher HbA1c levels than people with diabetes who don't have IDA. However, other studies have found the opposite, which means that monitoring these people with HbA1c could be misleading because their real HbA1c level could be less or more than the true value. Anemia caused by a lack of iron and diabetes is a widespread health concern. Remember that iron deficiency is a significant factor in diabetes diagnosis and therapy. Research has also shown that iron deficiency treatments can fix heart and kidney problems caused by diabetes. Even though this topic has only been studied in a few studies, many of which had a relatively small sample size, it is evident that more research into the relationship between anemia and HbA1c is warranted. As demonstrated by the studies discussed, more evidence is needed to guide doctors and scientists on handling anomalies in erythrocyte indices in clinical practice. While more information is being collected, we've come up with a few suggestions for making it easier to use. The most pressing unanswered problems are the potential impacts of anaemia and erythrocyte abnormalities on the accuracy of diabetes diagnosis using HbA1c in the general population. A more all-encompassing view of potential therapies can help researchers get more precise results when designing future experiments. Also, it might be easier to show negative correlations with a bigger sample size and a more extended research period. With a large sample size and the most up-to-date lab methods, a thorough study is the need of the hour.

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Clinical Proforma

Particulars of the patient

1. Name:	3. Sex:	5. D.O.A
2. Age:	4. Occupation:	6. D.O.D

History:

Presenting complaints (with duration, onset, associated factors)

1. Polyuria	7. Bladder/bowel incontinence
2. Polyphagia	8. Impotence
3. Polydypsia	9. Postural dizziness
4. Weight loss/gain	10. History of significant cardiovascular / cerebrovascular disease / thyroid disorder.
5. Nocturnal diarrhoea/constipation	
6. Hypoglycaemic unawareness	

Past History: History of Tuberculosis, Diabetes, CAD, COPD, Asthma, Seizures.

Family history : Special consideration to HTN, DM, TB, CAD, CVA

Personal History:

1. Dietary	3. Bladder & bowel	5. Alcohol
2. Sleep	4. Smoking-	6. Treatment History

General Physical examination:

1. Built	4. BP
2. Nutrition	5. Pulse
3.Pallor/Icterus/Clubbing/Cyanosis/Lymphadenopathy/Oedema	6. Respiratory Rate
	7. JVP

Systemic Examination:

CVS: Inspection, Palpation, Percussion , Auscultation

CNS: Higher functions, Sensory System (including Parietal lobe sensations)

Motor System (including reflexes, abnormal movements), Cranial Nerves, Cerebellar signs, Meningeal irritation

Respiratory: Inspection, Palpation, Percussion, Auscultation

Abdominal: Inspection, Palpation, Percussion, Auscultation

Investigations:

1. Fasting Blood glucose

2. Post Prandial Blood Glucose

3. CBC

4. Peripheral Blood Film

5. HbA1c

6. Iron Profile – RBC indices. (MCV, MCH, MCHC),

- S. iron, S. ferritin. TIBC

INFORMED CONSENT

I _____ Son/Daughter/Wife of _____ resident of _____.

hereby declare that I give my full, free and voluntary informed consent in the thesis "**To study iron profile in diabetes mellitus and its relation with HbA1c**''

Dr._____ has informed me to my full satisfaction, in the language I understand, about the purpose, nature of study and various laboratory investigations for the study to be carried out. I have been informed about the duration of the study and instructions to be followed during the study period.

I give full consent for being enrolled in the above study and I reserve my rights to withdraw from this study, whenever I wish without prejudice of my right to undergo further treatment at Santosh Hospital, Ghaziabad U.P.

Patient's/ Patient's relative's signature
Or thumb impression

Doctor's signature

Name:

Date:

We have witnessed that the patient signed the above form in the presence of his free will after fully understanding its content.

Signature of Witness

Name

Signature of Investigator
Name: Dr. PRABHJOT SINGH
Designation: PG Department of General Medicine
Contact No.- 9814888702

संतोषमेडिकलकॉलेजएवंअस्पताल (गाजियाबाद)

सहमतिपत्र (सूचित)

मैं _____ बेटा / बेटी /पत्नी_____

निवासी _____ घोषणा करती हूं कि मैं डॉ. _____, ने मुझे मेरी भाषा में अपने अध्ययन **To study iron profile in diabetes mellitus and its relation with HbA1c** के उद्देश्य के बारे में, और अध्ययन के दौरान अपनाई जाने वाली विभिन्न प्रयोगशाला जांच के बारे में सूचित कर दिया है। मुझे अध्ययन की अवधि और उसके दौरान अपनाए जाने वाले निर्देश भी मेरी भाषा मे समझा दिए गए है| मैं उपरोक्त अध्ययन में बिना किसी दबाव के दाखिला ले रहा हूं और पूर्ण सहमति दे रहा हूं| सन्तोष अस्पताल, गाजियाबाद में अपने आगे के उपचार पर बिना प्रतिकूल प्रभाव डाले इस अध्ययन से और प्रयोगशाला जांच की प्रकृति से मैं जब चाहूँ बाहर जाने के अपने अधिकार को सुरक्षित रख रही हूं।

रोगी / रोगी के रिश्तेदार के हस्ताक्षर डॉक्टर के हस्ताक्षर

नाम दिनांक:

मेरी उपस्थिति में मरीज ने पूरी तरह से डॉक्टर के बताए गए अध्ययन और निर्देशों को समझने के बाद अपनी स्वतंत्र इच्छा से ऊपर के फार्म पर हस्ताक्षर किए है।

हस्ताक्षर नाम: प्रभजोत सिंह

पदनाम: पीजी

आयुर्विज्ञान चिकित्साविभाग

PATIENT INFORMATION SHEET

1. OPD no:
2. Name:
3. Age:
4. Sex:
5. Address:
6. Phone number:

We invite you / your patient to participate in the research study titled study of being conducted in Santosh Medical College and Hospitals, Ghaziabad.

In accordance with the rules of ethical committee, a written consent will be taken. The relevant history will be asked and clinical examination of the patient will be done. Only the results of the investigations that you / your patient has already underwent as standard of care for such condition, are required for the study and no additional investigation will be done for the study. Special investigations, if any, will be sent as per the discretion of the treating physician and no additional investigation will be conducted for the purpose of the study You / your patient identity will be kept confidential throughout the study and thereafter. You are free to withdraw from the study any time without any loss of rights to undergo treatment in this hospital.

For any further questions regarding the study you can contact the investigator of study at the following number

Dr. PRABHJOT SINGH

+91-9814888702

LIST OF ABBREVIATIONS

IDA	Iron Deficiency Anemia
HB	Hemoglobin
HbA1c	Glycosylated Hemoglobin
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
Fe	Iron
DM	Diabetes Mellitus
CKD	Chronic kidney disease
EPO	Erythropoeitin
GFR	Glomerular Filtration Rate
MDRD	Modified Diet For Renal Disease

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